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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,873	09/05/2003	Shyam S. Mohapatra	USF-182XC1	6872

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EXAMINER	
LIETO, LOUIS D	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/655,873	MOHAPATRA ET AL.	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-9,11,12,14,15,18-21,23-31 and 43-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-9,11,12,14,15,18-21,23-31 and 43-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *9/05/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/05/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 4/20/2006 is acknowledged. Claims 1-4, 6-9, 11, 12, 14, 15, 18-21, 23-31, and 43-57 are pending. Claims 1,4,and 43, were amended. New claims 58-65 were added. Claims 1-4, 6-9, 11, 12, 14, 15, 18-21, 23-31, and 43-57, and 58-65 are under consideration. An action on the merits follows.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/20/2006 has been entered.

Claim Objections

Claims 46, 48 and 51 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The rejection of claims 1, 4,9,11,14,15,18, 20, 27,28,30,31,43-48,51-56 under 35 U.S.C. 102(a) as being anticipated by Kumar et al. {Kumar et al. (2001) J. Allergy Clin Immunol; 108:402-8} is withdrawn in view of Dr. Mohaptra's declaration filed under 37 CFR 1.132.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 2,3,6,8,12,21,23,24,26,29,50, and 57 under 35 U.S.C. 103(a) as being unpatentable over Kumar et al. {Kumar et al. (2001) J. Allergy Clin Immunol; 108:402-8}, further in view of Hogan et al. {Hogan et al. (1998) Eur. J. Immunol. 28: 413-423}, Carroll et al. {Carroll et al. (1998) J. of the Nat. Canc. Inst. 90:1881-1887}, Genbank Accession No: B38957 {Accession No: B38957, now gi: 1082578 (12.01.2000), Genbank Accession No: X13274 {Accession No: X13274 (11.15.1994)}, US Patent Application No: 2003/0138404 (7.24.2003), priority to (7.14.1995), and European Patent Application No. EP343388A2 (11.29.1989), is withdrawn in view of Dr. Mohaptra's declaration filed under 37 CFR 1.132.

Claims 1-4, 6-9, 11, 12, 14,15, 18-21, 43-45,47,49,50,52, and 53-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. {Hogan et al. (1998) Eur. J. Immunol. 28: 413-423}, and further in view of Li et al. {Li. et al. (1996) J. Immunol. 157: 3216-3219} US patent 6,693,086 (2.17.2004) priority to (6.25.1998), hereafter referred to as Dow et al, and O'Donnell et al. {O'Donnell (1999) J. Immunol. 163:4246-4252}. This new rejection is necessitated by applicant's amendments to the claims.

Hogan et al teaches the construction and administration of a vaccinia virus encoding the p35 subunit and the p40 subunit of mouse IL-12 operably linked to a promoter (pg. 420, Section 4.7). Said sequences are biologically equivalent to SEQ ID NOs: 7 & 8 (human p35 subunit) and SEQ ID Nos: 9 & 10 (human p40 subunit). Further, Hogan teaches that in mice sensitized with OVA (pg. 420, Section 4.2), IL-12 gene delivery inhibits airway inflammation (pg. 415, Figure 1, Col. 1), increases the levels of IFN-γ (Th-1 type cytokine) and decreases the levels of IL-4 and IL-5 (Th-2 type cytokines) expressed in lung cells (pg. 416, Figure 2) after intranasal administration in gelatin saline (pg. 420, Section 4.7). Hogan et al. teaches that IL-12 protects against lung damage by increasing the levels of IFN-γ expressed (pg. 418, col.1). Finally, Hogan et al teaches that viral titers in the mouse lung peaked at day 3 after administration of vaccinia encoded IL-12 (pg. 417, Figure 4), which indicates that the viral nucleic acid was contained within a cell. Hogan et al. does not teach the administration of IFN-γ encoded within the same vaccinia virus.

Li et al. supplements Hogan et al. by providing guidance on the construction of a plasmid vector encoding IFN-γ and operably linked to a promoter; followed by mucosal administration of the vector to mice suspended in lipofectamine (Abstract, pg. 3216, Col. 1, Materials and

Methods). Said plasmid encoded IFN-γ is biologically equivalent to SEQ ID NOs: 11 & 12 (human IFN-γ). Li et al. shows that the IFN-γ is expressed in higher levels of treated mice and that the vector is contained within mouse lung cells (pg. 3217, Figure 1). Finally, Li et al shows that administration of vector encoded IFN-γ inhibits pulmonary allergic responses in mice sensitized with CA (pg. 3217 col. 1) and leads to a significant decrease in eosinophilia (pg. 3218, Figure 2, Col 2.).

Dow et al. supplements Hogan et al. by providing guidance on a method for systemic immune activation for protecting a mammal from a disease associated with allergic inflammation (Abstract). Dow et al. teaches that eliciting an immune response that alters the overall immune response in a mammal can be particularly effective in the treatment of allergic inflammation (col. 14, lines 40-65). For example, elicitation of a Th1-type response in a mammal that is undergoing a Th2-type response. Th2-type T lymphocytes can be characterized by their production of one or more cytokines, collectively known as Th2-type cytokines, such as interleukin-4 (IL-4) or interleukin-5 (IL-5) (col. 14, lines 40-65). Dow et al. teaches the administration of expression vectors using pCR3.1, which encode IL-12 or IFN-γ, via liposomes, to mice (col. 37, lines 1-60). The pCR3.1 vector from Invitrogen has a CMV promoter operably linked to the insert (see vector map). Wherein, the plasmids may be administered intravenously (Examples 10 and 11, col. 47, 48).

O'Donnell et al. supplements Hogan et al. by providing guidance on a method for the treatment of bladder cancer by administering the antigen bacillus Calmette-Guerin (BCG) concurrently with rIL-12 in a pharmaceutical composition to a mouse model (Abstract, pg. 4247, Materials and Methods). Wherein administration of the antigen with IL-12 dramatically

increases IFN-γ production (Abstract). O'Donnell et al. teaches that an burst in TH-1 cytokine production underlies the effectiveness of BCH therapy (pg. 4246, col.1). Further, O'Donnell et al. teaches that this method may provide a useful immunotherapy for humans, especially the 30-50% of patients that fail to respond to BCG alone (pg. 4246, col. 2; pg. 4251, col. 2).

Based on the guidance provided by Hogan et al. on a method of administering vaccinia virus encoded IL-12 to mice sensitized with antigen to reduce allergic lung inflammation the teachings of Li et al. on a method of administering plasmid encoded IFN-γ to mice sensitized with antigen to reduce allergic lung inflammation and the teachings of Dow et al. on the use of plasmids encoding IL-12 or IFN-γ to reduce allergic inflammation, it would be *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Hogan et al. with the guidance of Li et al. by administering vaccinia viral or plasmid vectors separately encoding IL-12 and IFN-γ intravenously or intranasally. Further in view of the teachings of O'Donnell et al. it would be *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to administer vaccinia viral or plasmid vectors separately encoding IL-12 and IFN-γ with BCG to treat bladder cancer in humans.

A practitioner in the art would be motivated to administer vectors encoding IL-12 and IFN-γ intranasally in order to increase serum IFN-γ levels above those produced by vector encoded IFN-γ or IL-12 alone thereby decreasing the eosinophila and levels of IL-4 and IL-5 cytokines, and producing better protection against allergic inflammation, such as lung inflammation. A practitioner in the art would be motivated to administer vectors encoding IL-12 and IFN-γ in order to increase TH-1 cytokine levels and to treat the 30-50% of patients that fail to respond to BCG alone.

The person of ordinary skill in the art would have a reasonable expectation of success because the administration of two vectors separately encoding IL-12 and IFN-γ with or without an antigen such as BCG would have been a minor and routine modification to the method of Hogan et al.

Response to Arguments

Applicant's arguments filed 4/20/2006 have been fully considered but they are not persuasive. Applicant argues that there is nothing in the cited references to suggest that administration of a nucleic acid sequence encoding IL-12 and a nucleic acid encoding IFN-γ would have a synergistic effect. The claims only require that when administered together the method results in an increase of TH-1 type cytokine production and a decrease of TH-2 type cytokine production within the patient. Further, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. The key issue at hand is whether a person of ordinary skill in the art would have been motivated to administer a nucleic acid sequence encoding IL-12 and a nucleic acid encoding IFN-γ. The art of record clearly shows that IL-12 was known to synergize with numerous cytokines such as IL-18 and IL-2 {Jong et al. (1997) J. Imuunol. 159:786-793, Abstract; Nakahira (2002) J. Imuunol. 168: 1146-1153, Abstract}. Similarly IFN-γ was also known in the art to interact synergistically with IL-2 and IL-6 {Adachi et al. (1999) J. Imuunol. 163 :4367-4374}. The synergistic activity

of various cytokines is a common phenomena in immunology and would have been an obvious, motivating and reasonably expected result from the administration of a nucleic acid sequence encoding IL-12 and a nucleic acid encoding IFN-γ to a patient. The ordinary practitioner would have known from the art that IL-12 and IFN-γ were capable of synergistic activity with other cytokines and this would have motivated her to combine them in the instant method in order to achieve the beneficial effect associated with increased production of TH-1 cytokines and decreased production of TH-2 cytokines. Therefore the rejection is maintained for reasons of record as stated above and in the office actions of 12/15/05 and 1/13/05.

No Claims Allowed

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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